REMARKS

Claim 39 has been amended in response to the Examiner's rejections of claim 39 under 35 U.S.C. §112, second paragraph, in the Office Action of June 2, 2005.

No new subject matter has been added by this amendment.

Claims 39-60 are currently pending in this application.

Claims Rejection – 35 USC § 112

Claims 39-60 are rejected, under 35 U.S.C 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "substantially absent" in claim 39 is considered indefinite because it is unclear as to the means of measuring the degree of "substantially".

Applicants submit that this rejection is rendered moot in view of the amendment.

Claim Rejection – 35 USC § 103

Claims 39-60 are finally rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,776,710 to Levine et al. ("Levine 710") and U.S. Patent No. 5,393,674 to Levine at al. ("Levine 674").

The claims are rejected for the reasons of record in the previous office action dated June 2, 2005.

The rejection is respectfully traversed. Applicants reiterate and incorporate by reference arguments previously set forth during prosecution of the current application.

Of the claims rejected, Claim 39 is independent with the remaining claims dependent thereon.

The presently claimed invention relates to methods of separating at least one target component, e.g., cells, from a biological sample. The method comprises (1) placing the sample in a separation container, (2) centrifuging the separation container containing the biological sample; and (3) aspirating the target component(s) from the separation container. The separation container contains at least two distinct sets of selection beads and a focusing device with at least one axial bore passage, though which the biological sample can flow while the separation container is being centrifuged. The focusing device is designed such that the density of the

focusing device matches, or is substantially equal to, the density of the target component(s) when the target components are bound to the first set of selection beads. Thus, after centrifugation of the sample in the separation container, the first set of selection beads, bound to the target components, and the focusing device will be located in approximately the same vertical position within the container. The target components within the biological sample bind to the first set of selection beads via an affinity binding agent on the surface of the selection beads. The second set of selection beads has a different affinity binding agent on the surface than the first set of selection beads, and will thus bind components within the biological sample other than the target component. Additionally, the second set of beads has a different density than both the focusing device and the first set of selection beads. Thus, after centrifugation of the sample in the separation container, the second set of selection beads, possibly bound to components other than the target components, will not be located in approximately the same vertical position as the focusing device.

The methods of the current invention thus provide a four-fold means of selecting for target components, e.g., cells, in a single container and in a single experiment. The first means of selection involves the positive selection of the cells by their ability to bind the affinity binding agent on the first set of selection beads. The second means of selection involves the positive selection of components, based upon their expected densities after binding to the first set of selection beads. The third means of selection involves the negative selection of cells by their ability to bind the affinity binding agent on the second set of selection beads. The fourth selection means involves the negative selection of components within the biological sample, based upon their densities after binding to the second set of selection beads. The methods of the current invention also result in elongating the target component layer, thus making it easier for a technician to extract the target layer without interfering contamination.

The applicant's invention is neither taught nor rendered obvious by the cited references.

The Examiner states that "The method of Levine '710 differs from the presently claimed invention by failing to include the step of removing the desired component...." Applicants respectfully disagree with this interpretation of Levine 710. Namely, the methods of Levine 710 result in the analyte being trapped, or sandwiched, and affixed to the surface of a tube insert. For example, Levine 710 states that "the analyte-capture binding material [is] coated ... on the float insert." (See col. 7, lines. 35-38). The relationship between the position of the analyte-binding

material and the target analyte is very different between Levine 710 and the currently claimed invention. That the analyte-binding material is affixed to a solid surface is at least one reason why Levine 710 fails to teach or even suggest removal of the analyte. Indeed, the methods of Levine 710 render the analyte affixed to a solid surface and, consequently, immobile and thus completely unavailable for removal. Indeed, the specification of Levine 710 discusses the analyte as being "captured" and refers to the analyte binding material as the "analyte-capture binding material." United States Patent No. 5,776,710, (col. 7, lines. 3-13; col, 7, lines. 36-37). In fact, it is because of these differences in mobility of the target analyte that one of skill in the art would not be able to modify the methods of Levine 710 to arrive at the claimed invention. Indeed, modifying Levine 710 to render the analyte-capture material mobile would render Levine 710 totally inoperable, as the analyte would not longer be affixed to specific portions of the inserts for detection or identification.

The Examiner states that "Levine '674 disclose a method for harvesting target cells from a centrifuged sample of blood ...." Office Action mailed June 2, page 5. The differences between the methods of the currently claimed invention and Levine 674 are so great as to render Levine 674 irrelevant. Indeed, Levine 674 does not teach, mention or even suggest that microbeads or particulate carriers be used in conjunction with the float. Thus, the methods of Levine 674 provide, at most, a density selection method for isolating target components from a biological sample. Practicing the methods of Levine 674 results in isolating components, including contaminants, from a biological sample, where the isolated components have similar densities. In contrast to Levine 674, and as discussed previously herein, the methods of the currently claimed invention provide at least a 4-fold selection means for isolating target components from a sample, based on densities and binding affinities. As a result, the methods of the currently claimed invention result in a much richer cell harvest with substantially lower levels of contaminants.

The Examiner states that "It would have been obvious ... to include the step of removing the desired component ... as taught by Levine '674 in the method of Levine '710." Office Action mailed June 2, 2005, page5. Applicants respectfully maintain the submission that there is no motivation in the references to combine them, and respectfully disagree with this assertion that the combination of Levine 710 and Levine 674 would render the currently claimed invention obvious.

To establish a case of prima facie obviousness, the Examiner must meet three criteria. First, the Examiner must show that the references upon which she or he relied teach every limitation of the currently claimed invention, In re Royka 490 F.2d 981, 985 (C.C.P.A. 1974). Second, the Examiner must show that there is some suggestion or motivation in the references themselves, or within the knowledge of one of ordinary skill in the art, to combine the references to arrive at the claimed invention. Lastly, the Examiner must show that there is a reasonable expectation of success in combining the references, and that this expectation of success is found in the references as well. In re Vaeck 947 F.2d 488, 493 (Fed. Cir. 1991). Applicants assert that the cited art, alone or in combination, does not teach each and every limitation of the currently claimed invention, nor do the references provide any teaching, suggestion or motivation to combine the cited art to arrive at the claimed invention, with a reasonable expectation of success. From the previous discussions of the differences between the currently claimed invention and the cited art, it should be readily apparent that the cited art does not and cannot teach each and every element of the currently claimed invention. Indeed, neither Levine 710 nor Levine 674, alone or in combination, teaches a method comprising the use of a float with an axial bore passage and microbeads that bind the target component.

Additionally, nowhere in the prior art is there a suggestion or motivation to combine Levine 710 and Levine 674 to arrive at the currently claimed invention. Indeed, one of skill in the art, reading Levine 710, could not look to Levine 674 to provide a removal step to the methods disclosed in Levine 710. As discussed herein, the methods of Levine 710 render the target analytes immobile and completely incapable of removal. Furthermore, modifying the methods of Levine 710, in an attempt to render the captured analyte more mobile and thus amenable to removal, would destroy the operability of Levine 710. Thus, there would be no motivation to combine the cited references, because the methods disclosed in the cited references can not be combined while still retaining their functionality. Furthermore, because the cited art does not contain any motivation to combine the cited references, the prior art can not possibly convey a reasonable expectation of success in combining the references to arrive at the claimed invention. And "[b]oth the suggestion [to carry out the claimed process] and the expectation of success must be founded in the prior art, ..." In re Dow Chemical Co., 837 F.2d 469, 473 (Fed. Cir. 1988). In contrast to a reasonable expectation of success, one of skill in the art would understand that the cited art could not be combined with any degree of success.

Neither Levine 710 nor Levine 674, alone or in combination, teaches each and every element of the claimed invention. In addition, one of skill in the art would, recognizing that the references could not be combined while still retaining operability, would never be motivated to combine Levine 710 and Levine 674 to arrive at the currently claimed invention. Finally, because Levine 710 and Levine 674 could not be combined in any operable means, one of skill in the art could not have a reasonable expectation of success in producing the currently claimed invention.

Applicants note Examiners' specific comments responding to Applicants' previous arguments, in the Office Action mailed June 2, 2005 paragraph 15, pages 8-10, and have the following comments.

First, the claimed method does not immobilize the target component as in Levine 710 but binds it to a "mobile" first set of selection microbeads. Unlike Levine 710, the target analyte component /microbead complex is still free to move about the tube during centrifugation and is available for removal once centrifugation is complete.

Second, regardless of the disclosed advantages of Levine 674, for the reasons above, there would still have been no motivation to combine the teachings of Levine 710 and Levine 674.

Third, given the disparate nature of Levine 710 and Levine 674, Applicants maintain their position as to the lack of reasonable expectation of success.

Accordingly, Applicants assert that the cited references fail to render the currently claimed invention obvious under 35 U.S.C. §103. Reconsideration and withdrawal of this rejection is earnestly solicited.

In view of the amendments and remarks herein, applicant submits the claims are patentably distinct over the prior art and allowable in form.

The Commissioner is hereby authorized to charge payment of any additional fees associated with this communication or credit any overpayment to Deposit Account No. 02-1666.

If the Examiner has any questions or comments relating to the present application, he or she is respectfully invited to contact Applicant's agent at the telephone number set forth below.

Respectfully submitted,

M Lindsey

Mark Lindsey
Registration No. 52,515
Agent for Applicant(s)
201 847 6262

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Becton, Dickinson and Company
1 Becton Drive, MC110
Franklin Lakes, New Jersey 07417-1880

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